35th Annual International Conference of the IEEE EMBS
Osaka, Japan, 3 - 7 July, 2013

An image guided treatment platform for prostate cancer photodynamic therapy

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Abstract—**This study describes a multimodality images based platform to drive photodynamic therapies of prostate cancer using WST 11 TOOKAD Soluble drug. The platform integrates a pre-treatment planning tool based on magnetic resonance imaging and a per-treatment guidance tool based on transrectal ultrasound images.**

Evaluation of the platform on clinical data showed that prediction of the therapy outcome was possible with an accuracy of 90 %.

I. Introduction

These last years, prostate cancer (PCa) detection and localization have increased thanks to use of Prostate Specific Antigen (PSA), the screening and the development of new prostate biopsies protocols based on multimodality imaging: magnetic resonance (MR) and transrectal ultrasound (TRUS). Also, today a growing number of small volume and low grade cancer foci are diagnosed in young healthy men. Standard treatments for prostate cancer such as surgery or radiation involve the whole gland, even if the tumor is localized. Despite their oncologic efficiency, radical treatment modalities are associated with significant morbidity (urinary and sexual dysfunction) and may be linked to useless overtreatment.

Active surveillance can be an alternative to radical treatment in this indication. However, this strategy induces important psychological stress for patients and it is often difficult for clinicians to propose this management option to young men with long life expectancies.

Today, a new treatment concept is emerging and is termed "focal therapy". The challenge of current focal therapy techniques is to treat only localized tumors sparing the rest of the prostate to minimize the potential morbidity. Photodynamic therapy (PDT) allows this kind of therapies and starts to be an alternative when dealing with early stage prostate tumors [1]. PDT depends on three components: a photosensitizer, light and oxygen. The success of the treatment relies on an optimal dosimetric planning. However, due to the tissue heterogeneity, light and drug distributions are difficult to estimate and thus planning is a complex task. Different studies focused on this issue. Some groups have proposed solutions based on analytical implementation of the photons diffusion equation (Wilson *et al.* [2], Altschuler *et al.* [3], Du *et al.* [4], Johansson *et al.* [5], Davidson *et al.* [6]). Other approaches are based on Monte Carlo simulation of photon transport [7].

In another method group, correlation between the necrosis and different factors such as in vivo photosensitizer photo-bleaching during PDT, energy fluence and irradiation time were studied to deduce mathematical models ([8], [9]).

WST11 TOOKAD Soluble® is an intravascular photosensitizer drug administrated to patient in the operating room and activated by light diffusing optical fibers inserted directly inside the prostate to target the focus. Clinical trials of WST11 are ongoing. A drug dose (4 mg/patient kg) was defined as optimal. It is activated using a wavelength of 753 nm. Light is delivered through cylindrical light diffusers at the rate of 0.15 W/cm during 1333 s. Fibers are placed within needles in the prostate and the diffusing tip of each fiber is positioned according to the security margins from the apex, the base and the capsule. Insertion is guided by transrectal ultrasound and a perineal template as in brachytherapy.

In this study, we describe a full treatment planning and guidance platform to drive PDT procedures with WST11.

II. Material and Methods

Figure 1 depicts the platform flowchart. It integrates two modules: a pre-treatment module based on MR imaging and a per-treatment module based on TRUS images.

A. Pre-treatment planning

Most previous studies aiming the development of treatment planning approaches for PDT, focused on the estimation of prostate tissue optical properties. However, light penetration in these tissues is heterogeneous due to the fact that prostate is composed of different parts: peripheral zone, central zone, transition zone and the fibromuscular stroma. Each part exhibits different tissue properties. Moreover, for PDT procedures, light is activated after drug injection which means that the original optical properties of tissues are altered by the drug presence into vasculature.

Starting for this assumption, we have introduced a model to estimate the outcome of PDT using WST11 [10]. This dosimetric model was optimized by the retrospective study of data from 28 patients enrolled in a phase II clinical study (NCT00975429). The aim of that clinical essay was the determination of the optimal treatment parameters: drug and light doses.

*Research supported by the French National Institute of Health and Medical Research (INSERM) and by the Steba Biotech Company (Paris, France).

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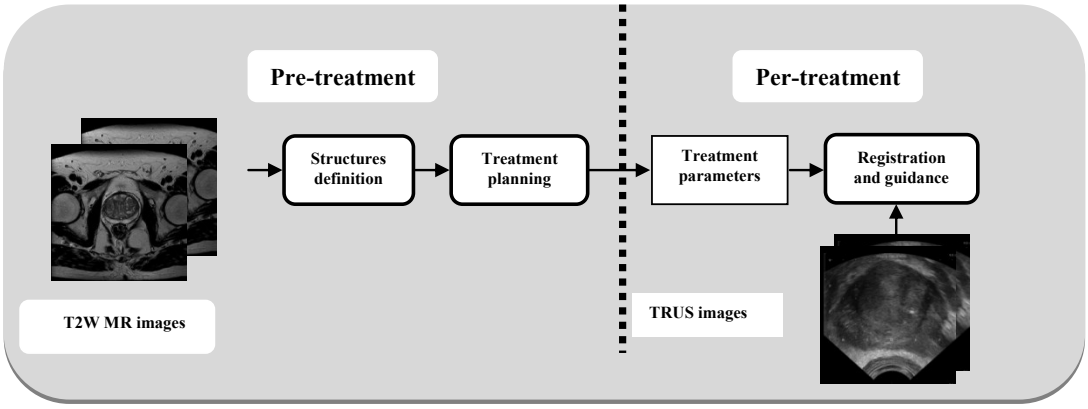
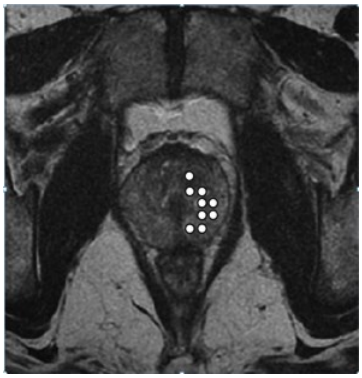


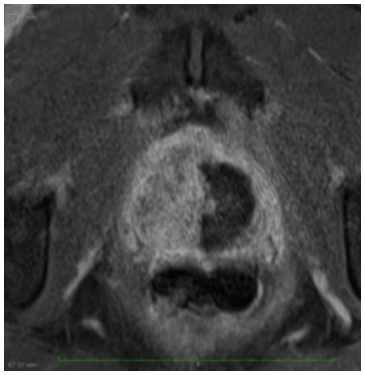
Figure 1. The pipeline of the platform using pre and per treatment images.

The model correlated the light treatment parameters used: number of fibers and for each fiber the length of its diffusing part, its positions inside the prostate and the result of the treatment: the necrosis volume, measured on dynamic gadolinium-enhanced magnetic resonance T1-weighted (T1W) images. Images were acquired one week after the therapy (figure 2).

(a)



(b)



(c)

Figure 2. Example of data collected from the phase II study. (a) An optical fiber with the light diffusing tip. (b) T2W MR image of the prostate showing the number and the positions of the optical fibers used (white circles). (c) Day 7 T1W MR image showing the left hemi-ablation necrosis.

The model allowed characterizing a unique fiber action radius of 6.5 mm which means that when a cylindrical diffuser with a diffusing part of length L mm is inserted in the prostate to activate the drug, it induces a pseudo cylindrical shaped necrosis with a length L and a 6.5 mm radius. Starting from this model, a treatment planning method was introduced ([10]).

For a given patient, using MR images, a treatment plan is prepared by structures definition (target and structures at risk as urethra) and the light dose by defining the light diffusers number, their lengths and their positions.

B. Treatment guidance using ultrasound images

Treatment planning is done on MR images before the procedure because this imaging modality allows, clear visualization of the structures of interest (the prostate gland, the peripheral zone, the rectum and the urethra) and in most cases, precise tumors cartography inside the prostate. Intra-operative MRI to guide the procedure may be effective, but it is an expensive due to materials compatibility and logistics issues.

The other option is to use real-time TRUS images. In this case, the planning data are transmitted to the therapist who has to introduce laser fibers inside the prostate using guidance of TRUS images. This procedure needs to equate the positions from pre-operative MR images to real-time TRUS. To deal with this issue, we have proposed a non-rigid registration scheme to match prostate MR and TRUS images using a geometric based method. It exhibits the advantage of reduction of the user interaction for landmarks initialization while guaranteeing satisfying registration quality (figure 3) [11]. Preliminary obtained results, on phantom and clinical images, of the approach were promising ([12]). In this study, we incorporate this registration module to the treatment planning platform to drive treatment guidance of PDT procedures.

The non-rigid registration transformation allows MR and TRUS images fusion and the light diffusers positions mapping from MR space to TRUS space. Light dose is then displayed on the actual TRUS images allowing to the urologist to have an estimation of the result with the current diffusers configuration or when deformations are too important to update the configuration.

III. Experimentations and Results

A. Data

Evaluation of the platform is realized using data acquired on 15 patients enrolled in the clinical studies conducted for the evaluation of WST11.

For each patient the following images were collected:

- Pre-treatment axial T2W MR images: these images serve to prepare the treatment planning.
- In the operating room, once the patient was placed in the treatment position, TRUS images are acquired. 3D calibration and reconstruction of the images are performed thanks to the brachy stepper used to move the ultrasound probe with a step of 5 mm.
- Gadolinium enhanced T1W MR images acquired at the day 7. These images allow measuring the necrosis volume. The necrosis is depicted as a devascularized area (as in figure 2-b).

B. The procedure

In pre-treatment conditions, using the T2W MR images, a radiologist delineates the prostate contours and defines the target to be treated. Target definition is mainly driven by the biopsies results. These volumes are used as input for the planning module optimization to determine the most suitable fibers configuration that maximizes light in the target while sparing the healthy areas of the prostate.

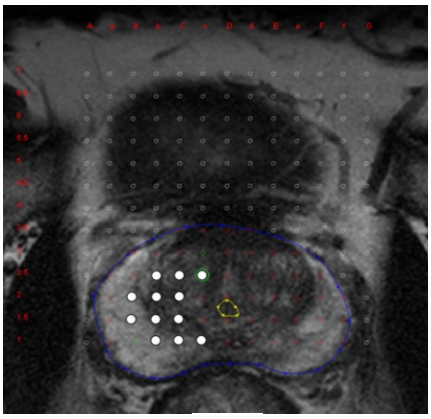
At the end of the optimization process, the number of diffusers to be used is computed and for each diffuser its position regarding an external template is estimated as well as the length of the diffusing parts (figure 3-a). Moreover, light distribution dose is displayed on the MR images (figure 3-b). This display allows the surgeon to estimate the treatment planning quality.

In the operating room, TRUS images are acquired as described previously. In order to help the surgeon to set the fibers as described in the treatment planning, the TRUS and the T2W images are registered and the fibers configuration is applied and updated using the TRUS images (figure 4).

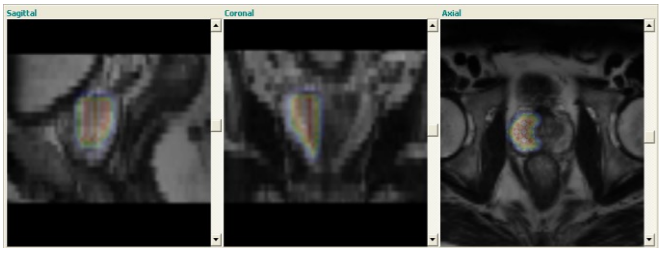
D7 MR images serve to estimate the necrosis volume. This volume is the ground truth.

C. Evaluation

Evaluation of the treatment planning and treatment guidance quality is done by measuring the planned necrosis volume and the real volume measured on the day 7 MR images. In order to take into account the fact that inflammation occurs and affects the volumes, swelling correction is done. First, the swelling ratio is computed as the ratio of the day 7 prostate volume and the pre-treatment prostate volume (typically in the range [1.15-1.2]). Then, the necrosis volume measured on the day 7 MR images is corrected by this ratio.



(a)



(b)

Figure 3. Example of treatment planning preparation for right hemi-ablation. Optimal fibers configuration contains 12 fibers. Each fiber poition is optimized regarding an external tempalte (the grid). This grid is used in the operating room to drive the fibers insertion. (b) 3D display of the corresponding light dose distribution.

D. Results

Table 1 summarizes the obtained results for the 15 patients:

TABLE I. Treatment Planning evaluation results

Patient	*Pre-treatment estimated necrosis volume (cm^3)*	*Day 7 measured necrosis volume (cm^3)*	*Ratio (%)*
1	16.1	17.7	91%
2	12.0	12.9	93%
3	21.9	24.9	88%
4	29.7	31.6	94%
5	8.3	9.6	86%
6	9.2	10.2	90%
7	23.7	26.1	91%
8	9.7	10.2	95%
9	26.2	30.8	85%
10	19.6	21.8	90%
11	25.5	28.0	91%
12	26.8	30.1	89%
13	35.3	41.1	86%
14	32.2	37.0	87%
15	14.9	16.0	93%
Mean			**90%**

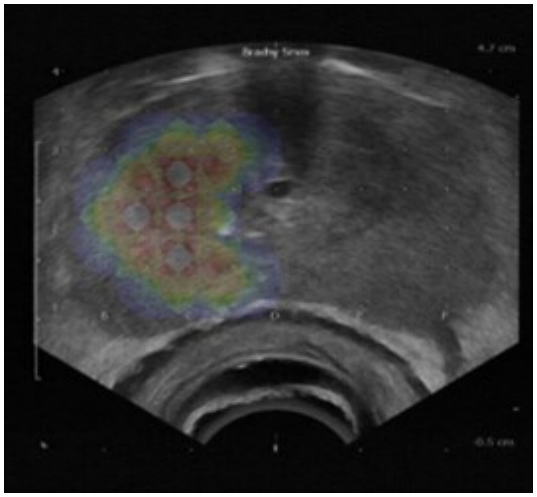


Figure 4. Ligt dose display on TRUS images after non-rigid registration of the images with the pre-treatment MR T2W images.

IV. Discussion – Conclusion

Photodynamic therapy is a promising technique to perform a focal treatment of some localized prostate cancers. Its clinical development and application is related to the development of dosimetric planning and guidance tools to make the method safe and efficient. In this study, we described a treatment planning platform to drive photodynamic procedures using WST 11 TOOKAD Soluble drug. The platform combines two modules. The first one is a pre-procedure treatment planning module that allows the optimization of the fibers array configuration to ensure the accurate light delivery in the target while sparing the healthy surrounded tissue. The planning is based on a unique light action model and an optimization algorithm ([10]).

The second module drives the treatment by elastic registration of the MR planning images with the intra-procedure TRUS images ([11]). Elastic registration allows compensating prostate deformation between the two modalities. Spatial transformation, resulting from the registration is used to map the fibers positions from the MR images to the TRUS images.

The platform was tested in clinical conditions to perform PDT procedures aiming two kinds of treatments: left or right prostate hemi-ablation and total-gland ablation (except the urethra). In both cases, the planning tools were able to predict the final necrosis with an average precision of 90 % (table 1). From this table, it appears that different target volumes were considered (from 9.6 to 41.1 cm^3). In each, case the model gave a good estimation (min 85%) of the final necrosis observed on the day 7 MR images.

Similar treatment planning platform were proposed previously to drive PDT procedures, however, in most cases the approaches used were based on the real time measurement of prostate optical properties. In addition to the fact that in most cases, they are not yet suitable for clinical practice due to the need of additional material as detectors, these approaches could be hampered by the variability of these properties.

Potentially, another approach could be applied to enhance the planning, it is the real time monitoring of the mechanisms. Indeed, the treatment results from the photosensitizer consumption. Photosensitizer photobleaching is an indicator of the efficacy of the treatment. Photobleaching can be determined by measuring the drug fluorescence [13]. However, dedicated and clinically conditions suitable material has to be developed.

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